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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/441,140	SOLOMON, BEKA	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *177 and 210-214* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *177 and 210-214* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *28 January 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 210-213 have been amended and new claim 214 has been added as requested in the amendment filed on 19 March 2007. Following the amendment, claims 177 and 210-214 are pending in the instant application.

Claims 177 and 210-214 are under examination in the instant office action.

Reissue Applications

Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 5,688,651 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

This application is objected to under 37 CFR 1.172(a) as lacking the written consent of all assignees owning an undivided interest in the patent. The consent of the assignee must be in compliance with 37 CFR 1.172. See MPEP § 1410.01.

A proper assent of the assignee in compliance with 37 CFR 1.172 and 3.73 is required in reply to this Office action.

The reissue oath/declaration filed with this application is defective (see 37 CFR 1.175 and MPEP § 1414) because of the following: The amendment to the claims dated 19 March 2007 are not supported by a proper supplemental reissue declaration under 37 CFR 1.175 (see MPEP § 1414.01). It is noted that the claims submitted on 19 March 2007 have been significantly amended from the claims as presented with the previous oath, i.e. new claim 214, directed to a method of making a therapeutic composition, has been added to the claims.

In accordance with 37 CFR 1.175(b)(1), a supplemental reissue oath/declaration under 37 CFR 1.175(b)(1) must be received before this reissue application can be allowed.

Claims 177 and 210-214 are rejected as being based upon a defective reissue oath under 35 U.S.C. 251 as set forth above. See 37 CFR 1.175.

The nature of the defect(s) in the oath is set forth in the discussion above in this Office action.

Receipt of an appropriate supplemental oath/declaration under 37 CFR 1.175(b)(1) will overcome this rejection under 35 U.S.C. 251. An example of acceptable language to be used in the supplemental oath/declaration is as follows:

> "Every error in the patent which was corrected in the present reissue application, and is not covered by a prior oath/declaration submitted in this application, arose without any deceptive intention on the part of the applicant."

See MPEP § 1414.01.

It is noted that more than one reissue application has been filed for reissue on U.S. Patent No. 5,688,651. Thus, the application is objected to under 37 CFR 1.177(a), which requires that all multiple reissue applications resulting from a single patent must include as the first sentence of their respective specifications a cross reference to the other reissue application(s). Accordingly, the first sentence of each reissue specification must provide notice stating that more than one reissue application has been filed, and it must identify each of the reissue applications and their relationship within the family of reissue applications, and to the original patent.

Information Disclosure Statement

A signed and initialed copy of the IDS paper filed 28 January 2008 is enclosed in this action.

Declaration under 37 CFR 1.131

Supplemental declarations

The declaration under 37 CFR 1.131 and the supplemental declarations (i.e., the Kohn, Hirsch and Browdy declarations) filed on 19 March 2007 are insufficient to establish that conception coupled with reasonable diligence was established in the United States from a date immediately prior to November 22, 1994 (i.e. November 14,1994) to the filing date of December 6, 1994. Therefore, the declarations are also insufficient to overcome the rejection of claims 177 and 210-213 under 35 U.S.C. 102(e) as being anticipated by Anderson et al., U.S. Patent No. 5,589,154 issued 12-21-1996 as evidenced by Solomon, Expert Opin Biol Ther, 2(8):907-917, 2002 as set forth previously.

While the Examiner does not challenge the content of the declarations or the content of Exhibits A-Z per se, the fact that "conception was communicated to the United States prior to November 22, 1994" does not establish that conception was in the United States. In addition, that the patent attorneys were preparing a patent application in the United States from a time immediately prior to November 22, 1994 through December 16, 1994 does not establish that reasonable diligence to the constructive reduction to practice occurred in the United States. In this case, conception, diligence as well as reduction to practice occurred in Israel (a WTO member country) before the invention was communicated to the United States in order for the invention to be described in a U.S. patent application.

Accordingly, MPEP § 715 (a) states, "Prior invention may not be established under this section before December 8, 1993, in a NAFTA country other than the United States, or before January 1, 1996, in a WTO member country other than a NAFTA

country" (Emphasis added; see 37 CFR 1.131). Since conception, diligence and reduction to practice occurred in a WTO member country, i.e. Israel, before January 1, 1996, prior invention may not be established under 37 CFR 1.131. Thus, for the purposes of applying prior art under 35 U.S.C. 102(e), the priority date for the instant application is the effective filing date of the instant application, i.e. **16 December 1994**. Accordingly, the Anderson et al. patent (U.S. Patent No. 5,589,154) is available as a prior art reference for the instant claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 177, 210, 211 and 214 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are directed to a therapeutic composition, comprising: a pharmaceutical formulation comprising (i) a pharmaceutically acceptable carrier and (2) (a) a genetically-engineered antibody that inhibits aggregation of beta-amyloid or

maintains the solubility of soluble beta-amyloid, or (b) a fragment of the genetically-engineered antibody of (a) that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody that (i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid and (ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen or recognizes an epitope within residues 1-28 of beta-amyloid, a method of making said composition and a composition wherein the antibody is a single-chain antibody.

The Examiner is unable to find any support in the disclosure as-filed for the instant limitation of "wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody." Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to identify sufficient written support in the original specification for the "limitation" indicated above. Applicant's remarks, in the response filed on 19 March 2007 do not provide sufficient direction for the written description of the above-mentioned limitation of claims 177, 210, 211 and 214. Here, Applicant alleges that support for the instant amendment to the claims is at col.10, lines 1-3 of the specification. This passage states "The present invention uses genetically-engineered antibodies obtained from such selected antibodies as protecting agents of in vivo aggregation of their antigen leading to production of a soluble and stabilized protein." However, this does not provide support for the limitation outlined above since an antibody, as disclosed in the specification, is

an amino acid molecule, which is structurally and functionally distinct from DNA, a nucleic acid molecule. Therefore, the claims encompass new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The rejection of claims 210 and 211 under 35 U.S.C. 102(a) as being anticipated by Bickel *et al*. (*Bioconiugate* 5(2): 119-125, March/April 1994) as further evidenced by Solomon, Expert Opin Biol Ther, 2(8):907-917, 2002 is maintained for reasons of record and as set forth below.

The rejection of claims 210 and 211 under 35 U.S.C. 102(b) as being anticipated by Stern *et al*. *Am J Pathol*., May 1989, 134(5):973-8 as further evidenced by Solomon,

Expert Opin Biol Ther, 2(8):907-917, 2002 is maintained for reasons of record and as set forth below.

In the response filed on 19 March 2007, Applicant asserts that claims 210 and 211 do recite specific structure that is not possessed by the antibodies of Bickel or Stern. Applicant asserts that the antibodies are further defined by the limitation "wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody that ...." Applicant concedes, “It may be true in the broad sense of the term ‘genetic engineering’ that monoclonal antibodies can be considered to have been genetically-engineered when they are produced, for example, by hybridoma technology that is genetic fusion of spleen cells and myeloma cells, which is a form of genetic engineering,” but alleges that claim 210 does not read on a standard murine monoclonal antibody that is obtained by standard hybridoma technology. Applicant asserts that since claim 210 requires that the genetically engineered antibody is obtained from DNA encoding a monoclonal antibody, "genetically-engineered antibody" is distinguished from "monoclonal antibody" by the claim language itself. Applicants alleges, "It must be something different from a monoclonal antibody if it is obtained from DNA encoding a monoclonal antibody.” Applicant alleges that the phrase "wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody" requires that DNA encoding the monoclonal antibody has been genetically-engineered after the monoclonal antibody has been initially produced and selected. Regarding fragments, Applicant alleges that if the antibody in the prior art is not a genetically-engineered

antibody obtained from DNA encoding a monoclonal antibody; it can contain no fragment of such a genetically-engineered antibody.

Applicant's arguments have been fully considered and are not found persuasive. Contrary to Applicant's assertion, the claims do not recite a specific structure that distinguishes the instant antibodies from the antibodies of Bickel or Stern. Broadest reasonable interpretation of claim 210 encompasses a monoclonal antibody as taught by the prior art of record. Specifically, claim 210(2) (a) requires "a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid," which Applicant admits can encompass a monoclonal antibody. The further limitation of "wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody" does nothing to change the embodiment of the claim, because a monoclonal antibody *is* a genetically-engineered antibody that is obtained from DNA encoding a monoclonal antibody. The Examiner does not agree with Applicant's assertion that "It must be something different from a monoclonal antibody if it is obtained from DNA encoding a monoclonal antibody." The Examiner also does not agree that the phrase "wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody" requires that DNA encoding the monoclonal antibody has been genetically-engineered after the monoclonal antibody has been initially produced and selected. Bickel's (and Stern's) AMY33 is a monoclonal antibody, which is a genetically-engineered antibody that is obtained from DNA encoding a monoclonal antibody. It is noted that all proteins that are not chemically synthesized are obtained from DNA. Moreover, as stated previously,

Stern is also on point to all monoclonals as noted in Table 1 of the reference. All of these antibodies were obtained via immunization with Abeta 1-28 peptide and were shown via ELISA to react specifically to the human beta amyloid BAPP 1-28 epitope. Accordingly, the antibodies meet the structural limitations of the claims. Regardless, the limitations of "wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody that (i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid and (ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen or recognizes an epitope within residues 1-28 of beta-amyloid" are product-by-process limitations. Bickel and Stern both teach the monoclonal antibody AMY33 and Solomon evidences the anti-aggregating or solubility promoting properties to the antibody. Since the product is the same as in the prior art, how it was made is irrelevant. If Applicant is relying on these limitations to distinguish the claimed product(s) from that disclosed in the prior art, the burden is on Applicant to show a nonobvious difference imparted by the method of making. A product made by any other process renders a product-by-process claim unpatentable. See In re Marosi, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983) and In re Thorpe, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985).

The rejection of claims 210-213 under 35 U.S.C. 102(b) as being anticipated by Gaskin *et al.*, J Exp Med, 1 April 1993, 177(4):1181-1186 as evidenced by Solomon, Expert Opin Biol Ther, 2(8):907-917, 2002 is maintained for reasons of record and as set forth below.

In the response filed on 19 March 2007, Applicant asserts the human monoclonal antibodies of Gaskin are not "genetically-engineered antibodies" in accordance with the language of claims 210 and 211 in view of the requirement that such a genetically engineered antibody be obtained from DNA encoding a monoclonal antibody. Applicant asserts that only claims 210 and 211 contain alternative language i.e., obtainable using residues 1-28 or recognizing an epitope within residues 1-28. Applicant asserts that the claims have now been amended to specify that the human monoclonal antibody is obtainable using "a peptide consisting of residues 1-28 of beta-amyloid as an immunogen," and that this certainly does not encompass any antibody that could not have been raised using a peptide consisting of residues 1-28, as is the case with Gaskin. Applicant alleges that the language of Gaskin makes clear that the antibody could not have been obtained using a peptide consisting of residues 1-28, since Gaskin notes, at page 1184, there is a contribution from the 29-40 region to the reactive epitope. Applicant thus concludes that there is a structural difference between antibodies that are obtainable using a peptide consisting of residues 1-28 and the antibodies of Gaskin.

Applicant's arguments have been fully considered and are not found persuasive. As stated previously, Gaskin et al. teach four human monoclonal antibodies, MRE310, 293, 267 and 148 which bind epitope 1-28 of human Aβ and would therefore also be suitably obtained thereby (a product by process limitation). Thus the antibodies of Gaskin meet the structural limitations of the claims (Figure 1; p. 1182). The Examiner agrees that only claims 210 and 211 recite the alternative language referred to above.

Regarding these claims, Gaskin evidences that the antibodies react to Abeta 1-28 and that an antibody is reactive to the antigenic epitope to which it binds is a long held art accepted principle. Regardless, that the claimed antibody "may be obtained by" is a product by process limitation not garnering weight where the prior art antibody is already evidenced to provide the recited structural constraints of binding Abeta 1-28. Thus, claims 212 and 213 are anticipated. Regarding Applicant's assertion that there is a contribution from the 29-40 region to the reactive epitope, the fact that the antibody may cross react with other portions or that other portions of a peptide molecule may contribute to epitope stability is immaterial where the antibody is already evidence to bind the requisite epitope. Better binding is not the subject of the claims and mere evidence that certain residues may stabilize such a binding interaction is not a teaching that negates anticipation where binding is evidenced. Accordingly, the reference teachings anticipate the claimed invention and the rejection is maintained.

The rejection of claims 210 and 211 under 35 U.S.C. 102(a) as being anticipated by Walker *et al.*, *Journal of Neuropathology and Experimental Neurology*, July 1994, 53(4):377-383 as evidenced by Solomon Expert Opin Biol Ther, 2(8):907-917, 2002 is maintained for reasons of record and as set forth below.

In the response filed on 19 March 2007, Applicant again asserts that the present claims do not read on monoclonal antibodies directly obtained using standard hybridoma technology. Applicant asserts that the present claims require that the

genetically-engineered antibodies be obtained from DNA encoding such monoclonal antibodies.

Applicant's arguments have been fully considered and are not found persuasive. As set forth above, the claims do indeed read on monoclonal antibodies directly obtained using hybridoma technology because a monoclonal antibody *is* a genetically-engineered antibody that is obtained from DNA encoding a monoclonal antibody. Accordingly, the rejection is maintained.

The rejection of claims 177 and 210-213 under 35 U.S.C. 102(e) as being anticipated by Anderson et al., U.S. 5,589,154 issued 12-21-1996 as evidenced by Solomon, Expert Opin Biol Ther, 2(8):907-917, 2002 is maintained for reasons of record and as set forth below. Furthermore, newly presented claim 214 is also subject to the instant rejection under 35 U.S.C. 102(e).

In the response filed on 19 March 2007, Applicant notes that the effective date of the Anderson patent as a reference is November 22, 1994 and that this date is less than a month prior to the application date applicable to the present application, December 16, 1994. Applicant alleges that the present invention was conceived prior to November 22, 1994, and that conception was communicated to the United States prior to November 22, 1994. Applicant alleges that this conception was linked by reasonable diligence of the patent attorneys preparing the application from a date immediately prior to November 22, 1994, through to the constructive reduction to practice on December 16, 1994. Applicant submits a declaration under 37 C.F.R. 1.131 from the present

inventor as well as several other declarations and Exhibits A-Z that support Applicant's allegation. Thus, Applicant asserts that Anderson is not available as a prior art reference.

Regardless, Applicant alleges that the patent does not anticipate the instant claims. Applicant alleges that none of the antibodies of Anderson can anticipate any of the present claims because Anderson does not teach any specific antibodies. Applicant asserts that Anderson may present a wish to know if certain antibodies may exist, but it certainly does not present an enabling disclosure for any antibody that satisfies his requirements. Applicant alleges that while a U.S. patent is presumed enabling for the claimed subject matter, the subject matter being relied on by the examiner is not claimed in Anderson, and thus there is no presumption that the disclosure with respect to the antibodies is enabling. Applicant also asserts, "While Anderson states at column 9, lines 30-40, that preferred biologically active fragments of A-beta peptide lack amino acid residues 29-42, there is no suggestion that all antibodies raised against an A-beta 1-28 fraction will bind to A-beta in such a manner as to prevent binding by either thrombin or a thrombolytic agent, such as tPA." Applicant alleges, "Nowhere in Anderson is it suggested what epitope of A-beta is the binding epitope for either thrombin or tPA. Certainly one of ordinary skill in the art reading Anderson would not expect that all antibodies raised against A-beta 1-28 might have these very special properties." Applicant asserts that the Solomon reference does not teach that all antibodies raised against A-beta 1-28 will have the properties required by the present claims. Thus, Applicant concludes that there is no certainty that any antibody found to

have Anderson's desired properties will necessarily have the properties required by the present claims. Applicant cites case law that allegedly supports the stance that inherency must be certain and not established by possibilities or probabilities. Further, Applicant cites Ex parte Skinner and puts emphasis on the statement, "Nevertheless, before an applicant can be put to this burdensome task, the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art."

Applicant's arguments have been fully considered and are not found persuasive. As set forth above, the Anderson patent is available as prior art since the declaration under 37 CFR 1.131 and the supplemental declarations (i.e., the Kohn, Hirsch and Browdy declarations) filed on 19 March 2007 are insufficient to establish that prior invention was established in the United States from a date immediately prior to November 22, 1994.

In response to Applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which Applicant relies (i.e., that there is no suggestion that all antibodies raised against an A-beta 1-28 fraction will bind to A-beta in such a manner as to prevent binding by either thrombin or a thrombolytic agent, such as tPA) are not recited in the rejected claim(s). Thus, it is not necessary that the artisan believe that AMY- 33 would have these properties.

Regarding Applicant's assertion that the Anderson patent is not an enabling anticipatory reference, Anderson's disclosure does not lack any element provided by the claims of the instant application, i.e., the instant claims require no more than is taught

by the Anderson patent. Specifically, at col.9, lines 4-8, the patent teaches that preferred binding agents of the invention are beta-amyloid antibodies and antibody fragments, including recombinant antibodies, single chain antibodies, antibody fusion proteins and chimeric antibodies. The patent teaches selection of the antibodies with screening methods performed with antibodies elicited in response to immunization with beta-amyloid peptide at col.9, lines 9-12. The patent teaches that the antibodies are obtainable using a peptide consisting of beta-amyloid residues 1-28 at col.9, lines 30-32. The patent teaches that the antibodies are of human and monoclonal form and include antibodies that are modified to become human i.e., are of chimeric or humanized form, generated via recombinant genetic engineering (col.11, line 21, col.12, lines 10-44). The patent also teaches formulation of the genetically-engineered antibodies with a pharmaceutical composition that is a therapeutic composition (col.15, line 65 – col.16, line 34). These antibodies would have had the functions recited in the claims, namely, inhibition of aggregation of beta-amyloid or maintenance of solubility of soluble beta-amyloid. Thus, as set forth above, the limitations of claim 214 have also been met by the Anderson patent. In addition, it is noted that working examples are not required for anticipation.

Regarding Applicant's arguments that inherency must be certain and not established by possibilities or probabilities, MPEP § 2112 IV states, "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte*

Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). Further, once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to Applicant to show an unobvious difference (see MPEP 2112 (V)). As stated previously, Solomon teaches that antibodies targeting the N-terminus of Aβ (residues 1-28) have anti-aggregating properties including solubilization of existing aggregates and inhibition of aggregation (p.909). Regarding Applicant's assertion that Solomon does not teach that all antibodies raised against A-beta 1-28 will have the properties required by the present claims, the reference necessarily teaches so. In Figure on p.909, Solomon refers to the "N-terminal region" of beta-amyloid as residues 1-28 and states that the "EFRH epitope of anti-aggregating antibodies" is "located at positions 3-6." At col.2 on p.909, Solomon teaches that investigation of a large panel of antibodies against various regions of the beta-amyloid peptide showed that only monoclonal antibodies targeting the N-terminal region of the beta-amyloid peptide exhibit anti-aggregating properties. Thus, the Examiner has provided a basis in technical reasoning to reasonably support the determination that the antibodies raised against residues 1-28, or N-terminal region, of the beta-amyloid peptide have the inherent properties as claimed, which necessarily flows from the teachings of the applied prior art. Now that the examiner has presented evidence and reasoning tending to show inherency, the burden has rightfully shifted to Applicant to show an unobvious difference, who is required to rebut the presumption of operability of the cited patent by a preponderance of the evidence. See Ex Parte D, 27 USPQ2D

1067, 1069 (BPAI 1993). Applicant is reminded that the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Moreover, the fact that it is possible to operate within the scope of the reference teachings and not obtain an operative result alone is not sufficient. In re Michalek, 162 F2.d 229, 74 USPQ 107 (CCPA 1947). Since the Anderson patent teaches all the elements of the claims (both expressly and inherently), the patent anticipates the claimed invention.

The rejection of claims 210 and 211 under 35 U.S.C. 102(e) as being anticipated by Suzuki et al., US 5,750,349 issued 5-12-1998 as evidenced by Solomon, Expert Opin Biol Ther, 2(8):907-917, 2002 is maintained for reasons of record and as set forth below.

In the response filed on 19 March 2007, Applicant asserts that Suzuki does not anticipate for the same reasons as discussed above for Stern, Bickel and Walker. Applicant asserts that claims 210 and 211 do not comprehend monoclonal antibodies, such as those of Suzuki, whose DNA has not been genetically altered after production by hybridoma technology.

Applicant's arguments have been fully considered and are not found persuasive. As set forth above, the claims do encompass monoclonal antibodies such as those of Suzuki. Thus, the rejection is maintained for the same reasons as set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 177, 212 and 213 under 35 U.S.C. 103(a) as obvious over either Bickel *et al., Bioconiugate* 5(2): 119-125, March/April 1994 or Stern et al., *Am J Pathol*., May 1989, 134(5):973-8, in view of Becker *et al*., European patent application, EP 0613007 A2 and Anderson et al., US 5,589,154 issued 12-21-1996 is maintained for reasons of record and as set forth below.

In the response filed 19 March 2007, Applicant asserts that Bickel and Stern do not suggest that the antibody thereof will inhibit aggregation of beta-amyloid or maintain the solubility of soluble beta-amyloid. Applicant asserts that the Becker reference has nothing to do with these functions. Applicant asserts that Becker discloses the desirability of finding conformationally specific antibodies that show a high level of specificity for the beta-amyloid peptide in a specific conformation, while showing

markedly less specificity for the same peptide having a different secondary structure. Applicant alleges that there is no reason to believe that AMY- 33 would have the very special properties required by Becker. Thus, Applicant alleges that there is no motivation to combine Stern and Bickel with Becker and no reasonable expectation of success. Regarding Anderson, Applicant asserts that this reference also requires very special properties for the antibody used therein, i.e. it must prevent the binding of thrombin or tPA to beta-amyloid. Thus, Applicant alleges that there is no reasonable expectation that the AMY-33 antibody of Bickel and Stern will prevent the binding of thrombin or tPA to beta-amyloid as required by Anderson. Applicant alleges that the fact that Anderson mentions 1-28 and AMY-33 is raised against 1-28 does not provide the requisite expectation that AMY-33 will prevent binding of thrombin or tPA to A-beta and that there are many epitopes in the 1-28 region.

Applicant's arguments have been fully considered and are not found persuasive.

Applicant's assertions that there is no motivation to combine or that there is no expectation of success in combing the prior art of record are inaccurate. In response to Applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which Applicant relies (i.e., that AMY- 33 shows a high level of specificity for the beta-amyloid peptide in a specific conformation, while showing markedly less specificity for the same peptide having a different secondary structure or that AMY-33 prevents the binding of thrombin or tPA to beta-amyloid) are not recited in the rejected claim(s). Thus, it is not necessary that the artisan believe that AMY- 33 would have these properties.

Only a reason, suggestion or motivation need appear in the cited prior art in order to combine references under 35 U.S.C. 103. Pro Mold Tool Col. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). Moreover, in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom. In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). As set forth above, Bickel's (and Stern's) AMY33 is a monoclonal antibody that meets the limitations of a genetically-engineered antibody that is obtained from DNA encoding a monoclonal antibody, as claimed. Since Becker *et al.* teach pharmaceutical formulations containing antibodies having specificity for the β-amyloid peptide, and since the reference teaches that chimeric, humanized, veneered, resurfaced or CDR-grafted antibodies, single-chain antibodies, and human monoclonal antibodies and fragments thereof are preferred for reduction of hyperimmunogenicity *in vivo* when used for treatment or for detection of amyloid plaques, the reference provides motivation to combine. Furthermore, at the time of filing, such genetic engineering methods, e.g., humanization of antibodies was well established in the art. Therefore, there is a reasonable expectation of success. Additionally, in response to Applicant's argument that there is no reasonable expectation that the AMY-33 antibody of Bickel and Stern will prevent the binding of thrombin or tPA to beta-amyloid as required by Anderson, the fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*,

227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Therefore, contrary to Applicant's allegation, it would indeed be obvious to combine the references under 35 U.S.C. 103 (a).

The rejection of claim 177 under 35 U.S.C. 103(a) as obvious over Gaskin *et al.*, *J Exp Med*, 1 April 1993, 177(4):1181-1186 in view of Becker *et al.*, European patent application, EP 0613007 A2 and Anderson et al., US 5,589,154 issued 12-21-1996 is maintained for reasons of record and as set forth below.

In the response filed on 19 March 2007, Applicant asserts that Gaskin does not disclose or suggest that its antibody will inhibit aggregation of beta-amyloid or maintain its solubility, nor does Gaskin suggest that its antibodies will have the conformationally specific properties wished for by Becker or will prevent the binding of thrombin to A-beta, as is required by Anderson. Applicant alleges that there would be no motivation to to use the antibodies of Gaskin therapeutically, there would be no motivation to change their form to that of a single chain antibody, as it would not be obvious to administer the antibodies of Gaskin in any form for *in vivo* administration, detection, and diagnosis of disease or for treatment as taught by either Becker or Anderson.

Applicant's arguments have been fully considered and are not found persuasive. As with the arguments for Bickel and Stern above, it is not necessary that the Gaskin reference teach or suggest that its antibody has the properties disclosed by Becker or Anderson. Gaskin provides strong motivation for providing the antibodies disclosed therein at least for diagnostic purposes *in vivo* (entire document, e.g. abstract).

As set forth previously, Gaskin et al. teach a human monoclonal antibody and composition of the requisite epitope specificity i.e., reacting with Abeta 1-28. The Gaskin antibody is not a single-chain, as claimed.

However, Becker *et al*. teach pharmaceutical formulations containing antibodies having specificity for β-amyloid peptide. The reference teaches antibodies and fragments of antibodies, including chimeric, humanized, veneered, resurfaced or CDR-grafted antibodies, single-chain antibodies as well as human monoclonal antibodies and genetically engineered monoclonal antibodies (p. 4 columns 5-6). These antibodies are noted to be of a preferred form for reduction of hyperimmunogenicity *in vivo*, e.g. when used for treatment or for detection of amyloid plaques.

Furthermore, Anderson et al. also teach administration of Abeta antibodies 1-28 of human, humanized and of single chain monoclonal form for treatment of vascular hemorrhaging and Alzheimer's disease and for diagnosis and labeling of amyloid plaques *in vivo*.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the antibody with the requisite epitope specificity of Gaskin with the single-chain form for *in vivo* administration, detection and diagnosis of disease as taught by Becker or Anderson. The person of ordinary skill in the art would have been motivated to make these modifications for treatment with reduced hyperimmunogenicity *in vivo*, as taught by Becker or Anderson. The person of ordinary skill in the art would have had a reasonable expectation of success because all of the references teach that the

antibodies would work. Thus, contrary to Applicant's allegation, it would indeed be obvious to combine the references under 35 U.S.C. 103 (a).

The rejection of claims 177 and 212-213 under 35 U.S.C. 103(a) as obvious over Walker *et al.*, *Journal of Neuropathology and Experimental Neurology*, July 1994, 53(4):377-383, in view of Becker *et al.*, European patent application, EP 0613007 A2 and Anderson et al., US 5,589,154 issued 12-21-1996 is maintained for reasons of record and as set forth below.

In the response filed on 19 March 2007, Applicant asserts that this rejection must fall for the same reasons as discussed above with respect to the other obviousness rejections and that there would have been no reasonable expectation of success that the 10D5 antibody of Walker would have the very special properties required by Becker or Anderson for therapeutic or diagnostic use.

Applicant's arguments have been fully considered and are not found persuasive. As set forth above for the other rejections under 35 U.S.C. 103(a), it is not necessary that there be a reasonable expectation of success that the 10D5 antibody of Walker would have the properties required by Becker or Anderson. As set forth previously, Walker et al., each teach the antibody and composition of the requisite epitope specificity. The Walker antibody is not a human monoclonal (as in claims 212-213) or single chain (as in claim 177).

However, Becker *et al.* teach pharmaceutical formulations containing antibodies having specificity for β-amyloid peptide. The reference teaches antibodies and

fragments of antibodies, including chimeric, humanized, veneered, resurfaced or CDR-grafted antibodies, single-chain antibodies as well as human monoclonal antibodies and genetically engineered monoclonal antibodies (p. 4 columns 5-6). These antibodies are noted to be of a preferred form for reduction of hyperimmunogenicity *in vivo*, e.g. when used for treatment or for detection of amyloid plaques.

Furthermore, Anderson et al. also teach administration of Abeta antibodies 1-28 of human, humanized and of single chain monoclonal form for treatment of vascular hemorrhaging and Alzheimer's disease and for diagnosis and labeling of amyloid plaques *in vivo*.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the antibody with the requisite epitope specificity of Walker with the single-chain form for *in vivo* administration, detection and diagnosis of disease as taught by Becker or Anderson. The person of ordinary skill in the art would have been motivated to make these modifications for treatment with reduced hyperimmunogenicity *in vivo*, as taught by Becker or Anderson. The person of ordinary skill in the art would have had a reasonable expectation of success because all of the references teach that the antibodies would work. Therefore, contrary to Applicant's allegation, it would indeed be obvious to combine the references under 35 U.S.C. 103 (a).

The rejection of claims 177 and 212-213 under 35 U.S.C. 103(a) as obvious over Suzuki et al., US 5,750,349, in view of Becker *et al.*, European patent application, EP

0613007 A2 and Anderson et al., US 5,589,154 issued 12-21-1996 is maintained for reasons of record and as set forth below.

In the response filed on 19 March 2007, Applicant asserts that this rejection must fall for the same reasons as discussed above with respect to the other obviousness rejections and that there would have been no reasonable expectation that the antibody of Suzuki could be successfully used for any of the purposes required by Becker or Anderson.

Applicant's arguments have been fully considered and are not found persuasive. It is not necessary that there be an expectation antibody of Suzuki would have the properties required by Becker or Anderson. As set forth previously, Suzuki et al. teach the antibody and composition of the requisite epitope specificity as set forth above. The Suzuki antibodies are not human monoclonals (as in claims 212-213) or single chain (as in claim 177).

However, Becker *et al*. teach pharmaceutical formulations containing antibodies having specificity for β-amyloid peptide. The reference teaches antibodies and fragments of antibodies, including chimeric, humanized, veneered, resurfaced or CDR-grafted antibodies, single-chain antibodies as well as human monoclonal antibodies and genetically engineered monoclonal antibodies (p. 4 columns 5-6). These antibodies are noted to be of a preferred form for reduction of hyperimmunogenicity *in vivo*, e.g. when used for treatment or for detection of amyloid plaques.

Furthermore, Anderson et al. also teach administration of Abeta antibodies 1-28 of human, humanized and of single chain monoclonal form for treatment of vascular

hemorrhaging and Alzheimer's disease and for diagnosis and labeling of amyloid plaques *in vivo*.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the antibody with the requisite epitope specificity of Suzuki with the single-chain form for *in vivo* administration, detection and diagnosis of disease as taught by Becker or Anderson. The person of ordinary skill in the art would have been motivated to make these modifications for treatment with reduced hyperimmunogenicity *in vivo*, as taught by Becker or Anderson. The person of ordinary skill in the art would have had a reasonable expectation of success because all of the references teach that the antibodies would work. Therefore, contrary to Applicant's allegation, it would indeed be obvious to combine the references under 35 U.S.C. 103 (a).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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